

WHAT IS CLAIMED IS:

1. A method of identifying from among a plurality of existing compounds a molecule that is useful as a copper-binding angiogenesis inhibitor and/or anti-cancer agent, which method comprises:
- (a) selecting a compound or a plurality of compounds with the following characteristics:
- 5 (i) a molecular mass of less than about 1000 Da,
- (ii) at least two sulfur atoms separated from one another by 2 or 3 atoms, and
- (iii) optionally, one or both of the sulfur atoms has a lone pair of electrons;
- (b) testing said compound or plurality of compounds selected in (a) for their ability to remove copper from the CuZnSOD (SOD1) enzyme or to inhibit the catalytic activity of SOD1, and selecting
- 10 one or more compounds with such copper-removing or enzyme-inhibitory activity; and
- (c) optionally, testing said compound or compounds selected in (b) for their ability to inhibit cell proliferation *in vitro*,

wherein a compound that has said characteristics of (a), tests positive for SOD1-inhibitory activity and, optionally, inhibits cell proliferation *in vitro*, is identified as being useful as said angiogenesis inhibitor and/or anticancer agent.

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2. The method of claim 1, wherein, the compound selected in selecting process (a) also has the ability to adopt a conformation that places the two sulfur atoms at a distance of between about 2Å and about 5Å.

3. The method of claim 2, wherein the compound selected in selecting process (a) has the ability to adopt a conformation that places the two sulfur atoms of a distance of between about 3.4Å and about 3.8Å.

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4. The method of any of claims 1-3 wherein selecting process (a) is performed computationally.

5. The method of any of claims 1-4, wherein the compound or compounds are tested in step (c) for inhibition of the proliferation of activated endothelial cells.

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6. The method of any of claims 1-4, wherein the compound or compounds are tested in step (c) for inhibition of the proliferation of tumor cells.

7. The method of any of claims 1-6 wherein the assay for SOD1 inhibitory activity is a biochemical assay.

8. The method of claim 7 wherein the biochemical assay comprises use of chromogenic water-soluble tetrazolium salts that yield a colored product.

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9. The method of claim 8 wherein said tetrazolium salt is WST-1.

10. The method of any of claims 1-9 wherein the compound or compounds are further tested in an assay of endothelial cell migration.

5 11. The method of any of claim 1-10 wherein the compound or compounds are further tested in an assay of endothelial cell growth.

12. The method of any of claims 1-11 wherein the compound or compounds are further tested for tumor growth inhibition in an *in vivo* assay.

13. The method of claim 11 or 12 wherein the assay is a Matrigel® plug assay.

10 14. The method of any of claims 1-13 wherein said compound inhibits inhibition of SOD1, cell migration, cell growth and/or tumor growth by at least about 10%.

15. The method of claim 14 wherein said compound inhibits inhibition of SOD1, cell migration, cell growth and/or tumor growth by at least about 25%.

16. The method of claim 15 wherein said compound inhibits inhibition of SOD1, cell migration, cell growth and/or tumor growth by at least about 50%.

15 17. The method of claim 16 wherein said compound inhibits inhibition of SOD1, cell migration, cell growth and/or tumor growth by at least about 70%.

20 18. A method of designing a copper-binding molecule that removes copper from SOD1, thereby inhibiting SOD1 enzymatic activity, and is therefore useful as an antiangiogenic and/or anti-cancer agent, the method comprising determining atomic constituents and conformational parameters of the molecule being designed such that the molecule

(a) has the following physicochemical characteristics:

- (i) a molecular mass of less than about 1000 Daltons
- (ii) at least 2 sulfur atoms separated from one another by 2 or 3 atoms
- (iii) optionally, one or both of the sulfur atoms has a lone pair of electrons;

25 (b) has the following biochemical characteristics:

- (i) removes copper from SOD1; or
- (ii) inhibits the catalytic activity of SOD1, and

(c) has one or more of the following effects on cells:

- (i) inhibits proliferation of activated endothelial cells *in vitro*,
- 30 (ii) inhibits proliferation of tumor cells *in vitro*;
- (iii) inhibits endothelial cell migration *in vitro* or *in vivo*;

(iv) inhibits tumor cell growth *in vivo*;
thereby designing said molecule.

19. The method of claim 18 wherein, the molecule being designed has the ability to adopt a conformation that places the two sulfur atoms at a distance of between about 2Å and about 5Å.

5 20. The method of claim 19 wherein, the molecule being designed has the ability to adopt a conformation that places the two sulfur atoms of a distance of between about 3.4Å and 3.6Å.

21. A method for making a copper-binding molecule that removes copper from SOD1, thereby inhibiting SOD1 enzymatic activity, and is therefore useful as an antiangiogenic and/or anti-cancer agent, which method comprises:

- 10 (a) designing the molecule in accordance with any of claims 18- 20;
(b) selecting a synthetic process that will produce said molecule and stabilize its structure;
(c) employing the synthetic process of (b) to synthesize the molecule,
thereby making the molecule.

22. The method of claim 21, further comprising:

- 15 (d) testing the molecule produced in step (c) for one or more of the following activities:
(i) removing copper from SOD1;
(ii) inhibiting catalytic activity of SOD1,
(iii) inhibiting proliferation of activated endothelial cells *in vitro*,
(iv) inhibiting proliferation of tumor cells *in vitro*;
20 (v) inhibiting endothelial cell migration *in vitro* or *in vivo*;
(vi) inhibiting tumor cell growth *in vivo*.

23. A method for removing copper from the SOD1 enzyme, comprising contacting a sample comprising SOD1 enzyme with an effective amount of a compound identified in accordance with the method of any of claims 1-4, or designed or made in accordance with the method of any of claims 18-22,
25 for a time sufficient for removal of the copper from said enzyme.

24. The method of claim 23 wherein the compound is selected from the group consisting of ATN-427, ATN-714, ANT-719 and ATN-722.

25. The method of claim 23 or 24 wherein said removing is *in vivo*.

26. A method for inhibiting the activity of the SOD1 enzyme, comprising contacting a sample comprising SOD1 enzyme with an effective amount of a compound identified as an SOD1 inhibitor in accordance with the method of any of claims 1-17, or designed or made in accordance with the method of any of claims 18-22, for a time sufficient for inhibition of said enzyme.

5 27. The method of claim 26 wherein the compound is selected from the group consisting of ATN-427, ATN-714, ATN-719 and ATN-722.

28. The method of claim 26 or 27 wherein said contacting is *in vivo*.

10 29. A method for inhibiting endothelial cell proliferation comprising providing to endothelial cells an effective amount of a compound identified as a proliferation inhibitor in accordance with the method of any of claims 1-17, or designed or made in accordance with the method of any of claims 18-22, for a time sufficient for inhibition of said proliferation.

30. The method of claim 29 wherein the compound is selected from the group consisting of ATN-427, ATN-714, ATN-719 and ATN-722.

31. The method of claim 29 or 30 wherein said providing is *in vivo*.